

# Research Methods Resources for Clinical Trials Involving Groups or Clusters

David M. Murray, Ph.D.

Associate Director for Prevention

Director, Office of Disease Prevention

National Institutes of Health

Medicine: Mind the Gap

December 13, 2017



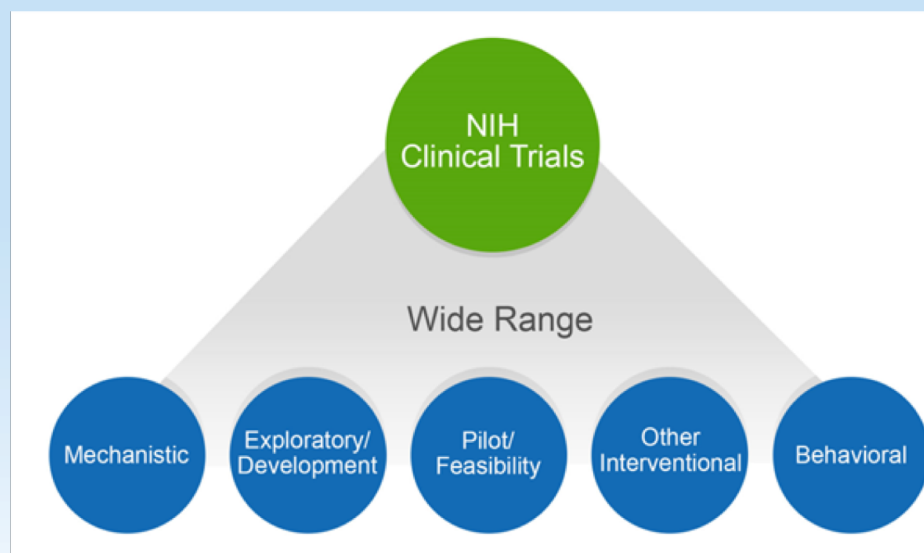
National Institutes of Health  
*Office of Disease Prevention*

# Agenda

- New NIH requirements for clinical trials
- Group- or cluster-randomized trials (GRTs)
- Individually randomized group-treatment trials (IRGTs)
- Changes to the Application Instructions
- Changes to the Review Criteria
- Research Methods Resources website

# NIH Definition of a Clinical Trial

- NIH published its revised definition of a clinical trial in 2014 after extensive public input.
  - A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.



# Does Your Study Meet the Definition?

- Does the study involve human participants?
- Are the participants prospectively assigned to an intervention?
- Is the study designed to evaluate the effect of the intervention on the participants?
- Is the effect that will be evaluated a health-related biomedical or behavioral outcome?
- If the answer to all four questions is yes, your study is a clinical trial under the NIH definition.

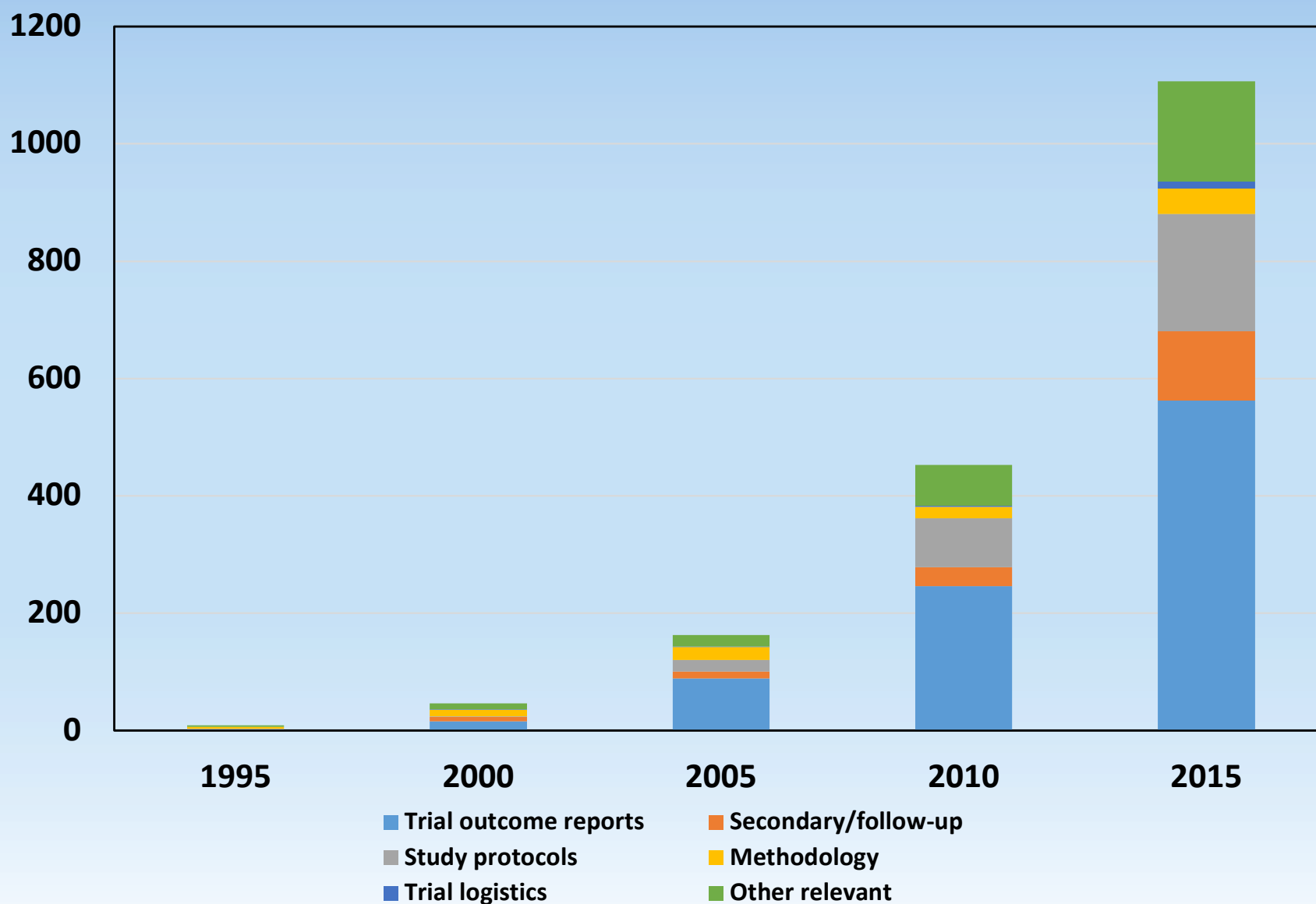
# New Requirements

- Information on the new Clinical Trial Requirements for Grants and Contracts is available at:
  - <https://grants.nih.gov/policy/clinical-trials.htm>
- The new requirements include
  - Training for good clinical practice
  - Single IRB for multi-site studies
  - Clinical trial specific funding opportunity announcements
  - Clinical trial specific review criteria
  - ClinicalTrials.Gov registration and reporting requirements
  - New application instructions and forms

# Three Kinds of Randomized Trials

- Individually Randomized Clinical Trials (RCTs)
  - Individuals randomized to study conditions with no connection among participants after randomization.
    - Most surgical and drug trials, some behavioral trials
- Individually Randomized Group Treatment Trials (IRGTs)
  - Individuals randomized to study conditions with some connection among participants after randomization.
    - Many behavioral trials
- Group-Randomized Trials (GRTs)
  - Groups randomized to study conditions with some connection among participants before and after randomization.
    - Human trials involving randomization of communities, physicians, worksites, clinics, churches, schools, etc.
    - Animal trials involving randomization of litters or other groups

# Pubmed Abstracts Identifying GRTs



# Impact on the Design

- Individually Randomized Clinical Trials (RCTs)
  - There is usually good opportunity for randomization to distribute potential confounders evenly, as most RCTs have  $N > 100$ .
- Individually Randomized Group Treatment Trials (IRGTs)
  - There may be less opportunity for randomization to distribute potential confounders evenly, as many IRGTs have  $N < 100$ .
- Group-Randomized Trials (GRTs)
  - There may be limited opportunity for randomization to distribute potential confounders evenly, as most GRTs involve a limited number of groups, often  $G < 25$ .



# Impact on the Analysis

- Observations on randomized individuals who have no connection are independent and are analyzed with standard methods.
- The members of the same group in a GRT will have some physical, geographic, social or other connection.
- The members of groups created for an IRGT will develop similar connections.
- Those connections create the expectation for positive intraclass correlation (ICC).
- That ICC violates the independence of errors assumption that underlies the usual analytic methods.

# Impact on the Analysis

- With positive ICC, the variance of the intervention effect will be increased.
- The df to estimate that variance will be based on the number of groups, and so are often limited.
  - This is almost always true in a GRT.
  - It can be true in an IRGT.
- Any analysis that ignores the extra variation or the limited df will have a Type I error rate that is inflated, often badly.
  - Type I error rate may be 30-50% in a GRT, even with small ICC
  - Type I error rate may be 15-25% in an IRGT, even with small ICC
- Extra variation and limited df always reduce power.

# The Warning

*Randomization by cluster accompanied by an analysis appropriate to randomization by individual is an exercise in self-deception, however, and should be discouraged.*

*Cornfield (1978)*

- Though Cornfield's remarks were addressed only to GRTs, they also apply to IRGTs.
- Cornfield J. Randomization by group: a formal analysis. American Journal of Epidemiology. 1978;108(2):100-2.

# State of the Practice in GRTs and IRGTs

- ODP has just finished a review of GRTs.
  - 123 GRTs in with cancer or cancer-related outcomes found in 81 journals 2011-15.
  - 54% documented appropriate methods for sample size.
  - 51% used only appropriate methods for analysis.
  - 30% used only inappropriate methods for analysis.
- Prior reviews have shown that the problems are even worse in IRGTs, with only about 5% using appropriate methods.
- Poor sample size and analytic practices contribute to the reproducibility problem.



# The New Application Guide and Review Criteria

- The Application Guide instructions for the new FORMS-E include several changes to alert investigators to the methodological issues inherent in GRTs and IRGTs.
- The clinical trials specific Review Criteria include similar changes.

# Application Guide FORMS-E

## Applications Due on or After 01-25-18

- PHS 398 Research Plan Form
- 3. Research Strategy
- 3.3. Approach
  - For trials that randomize groups or deliver interventions to groups, describe how your methods for analysis and sample size are appropriate for your plans for participant assignment and intervention delivery. These methods can include a group- or cluster- randomized trial or an individually randomized group-treatment trial. Additional information is available at the Research Methods Resources webpage.

# Application Guide FORMS-E

## Applications Due on or After 01-25-18

- PHS Human Subjects and Clinical Trials Information
- 4.2. Study Design
- 4.2.a. Narrative Study Description
  - Enter a narrative description of the protocol. Studies differ considerably in the methods used to assign participants and deliver interventions. Describe your plans for assignment of participants and delivery of interventions. You will also need to show that your methods for sample size and data analysis are appropriate given those plans. For trials that randomize groups or deliver interventions to groups, special methods are required; additional information is available at the Research Methods Resources webpage.

# Application Guide FORMS-E

## Applications Due on or After 01-25-18

- PHS Human Subjects and Clinical Trials Information
- 4.4. Statistical Design and Power
  - You will need to show that your methods for sample size and data analysis are appropriate given your plans for assignment of participants and delivery of interventions. For trials that randomize groups or deliver interventions to groups, special methods are required; additional information is available at the Research Methods Resources webpage.



# NOT-OD-17-118 New Review Criteria for Research Projects Involving Clinical Trials

## ■ Approach

- Study Design. Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research?  
**Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results?** Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

# NOT-OD-17-118 New Review Criteria for Research Projects Involving Clinical Trials

## ■ Approach

- Data Management and Statistical Analysis. **Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions?** Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

# Clinical Trials Protocol Templates

- There are two trans-NIH templates
  - NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template
  - NIH Behavioral and Social Intervention Clinical Trial Protocol Template
- ODP has recommended adding language consistent with the new material in the Application Guide.
  - Delineation of any expected interaction among participants
  - Tracking any changes in the structure of the groups or clusters
  - Reporting details for sample size estimation to address clustering
  - Reporting details for analytic methods to address clustering
- ODP will reach out to ICOs to suggest similar language for ICO-specific templates.



Research Methods Resources Website:  
**<https://researchmethodsresources.nih.gov>**

Send Questions To:  
**[rmr@od.nih.gov](mailto:rmr@od.nih.gov)**

# The Effect of a Weight Loss Intervention on BMI

- We plan to implement the intervention in churches and will measure BMI in 25 participants per church at both pretest and posttest.
- We expect that the average BMI at pretest to be 30 and the standard deviation to be 6.
- We want to have 80% power with a 5% type 1 error rate to detect a reduction of 5%, or 1.5 BMI units.
- We expect the pretest-posttest correlation in BMI to be 0.7.
- We plan a mixed-model ANCOVA, with regression adjustment for the pretest BMI; as such, we expect to explain 49% of the variance in the outcome by adjusting for the pretest BMI.
- To be conservative, we assume no benefit for regression adjustment on the group component of variance.



Research Methods Resources Website:  
**<https://researchmethodsresources.nih.gov>**

Send Questions To:  
**[rmr@od.nih.gov](mailto:rmr@od.nih.gov)**

# The Effect of an Intervention to Increase Colon Cancer Screening

- We plan to implement the intervention in community health clinics and will verify up-to-date colorectal cancer screening via chart review in 50 participants per clinic at posttest.
- We expect that 40% of adults in the population are up to date.
- We want to have 80% power with a 5% type 1 error rate to detect a relative increase of 30%, from 40% to 52%.
- We will base the variance on the average proportion, 46%.
- We plan a mixed-model ANCOVA, with regression adjustment for covariates; We expect to explain 20% of the participant level variance and 10% of the clinic level variance.
- We do not plan to match or stratify clinics a priori.



Research Methods Resources Website:  
**<https://researchmethodsresources.nih.gov>**

Send Questions To:  
**[rmr@od.nih.gov](mailto:rmr@od.nih.gov)**